

Classic Hodgkin Lymphoma presenting as ANA positive chronic papular urticaria like skin lesions – A case report

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Abstract

The skin acts as a natural barrier between internal organs and the external environment. Many haematological neoplasms occur in the skin as a primary malignant transformation, as secondary involvement, or as paraneoplastic cutaneous manifestations. Malignant skin involvement in Hodgkin lymphoma is uncommon while paraneoplastic cutaneous involvement can occur as eczema, pruritus, erythema nodosum, and ichthyosiform atrophy.¹

This case report describes a 25-year-old woman with a persistent pruritic rash, who was treated as chronic papular urticaria, before finally being diagnosed as Classic Hodgkin Lymphoma. This highlights the challenge of early diagnosis of cutaneous manifestations of Hodgkin lymphoma and the importance of considering malignancies in refractory dermatological conditions. This case also suggests a potential role for ANA patterns as diagnostic markers in Hodgkin lymphoma.

Key words: chronic papular urticaria, classical Hodgkin lymphoma, anti-nuclear antibodies

Introduction

Classic Hodgkin Lymphoma (CHL) is a malignancy of the lymphatic system characterized by the presence of Reed-Sternberg cells within the lymph nodes. While the hallmark of Hodgkin Lymphoma (HL) is lymphadenopathy, it can also present with cutaneous manifestations mimicking common skin

conditions.¹ Therefore, in a patient with a treatment resistant dermatological condition, a high degree of suspicion is necessary about the possibility of an underlying malignancy. Although anti-nuclear antibodies (ANA) are commonly described in the diagnosis of systemic autoimmune conditions,² a significant incidence of ANA has been shown in patients with non-Hodgkin's lymphoma (NHL).³ However, the identification of ANA patterns in HL and predicting prognosis needs further evidence.

Case history

A 25-year-old previously well woman presented with an itchy skin rash for a duration of 4 months. The rash appeared 4 months ago, which was of gradual onset, starting in both arms and legs. (Figure 1) It appeared as a papulonodular rash which was pruritic. She noticed that some lesions disappeared while new ones appeared, and the face, scalp, and buttock areas were spared. The rash did not worsen with exposure to sun or cold. A diagnosis of chronic papular urticaria was made by the dermatology team and she was started on emollients and antihistamines which did not alleviate the rash or the pruritus. Later, she was prescribed oral prednisolone for two weeks, after which the rash disappeared. However, one week after stopping prednisolone, the itchy rash reappeared involving both arms, legs, upper back, and upper trunk.

Three months after the onset of the rash she noticed enlargement of cervical lymph nodes, more prominent on the left side of the neck. Initially they

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were painful, but with time they became painless. She had not noticed any enlarged axillary or inguinal lymph nodes. There was no fever, night sweats, joint pains, or oral ulcers but she complained of hair loss. Her appetite was normal and there was no loss of weight. She could not recall any history of insect bites and there were no pets at home.

At the age of 15, the patient had undergone an appendicectomy and the histology revealed evidence of inflammation. She had not taken any over-the-counter medications and denied any drug abuse. She did not have any known allergies. She was unmarried and denied high-risk sexual behaviors.

On examination, the patient was not pale or icteric. She had a papulonodular rash involving both upper limbs (excluding the palms), bilateral thighs, upper chest, and upper back of the chest. There were painless cervical lymph nodes in the submental and bilateral posterior auricular regions. No axillary or inguinal lymph nodes were palpable. Her pulse rate was 88 bpm, blood pressure was 110/70mmHg, and the rest of the cardiovascular system examination was normal. No hepatosplenomegaly was detected during the abdominal examination, and respiratory and neurological examinations were unremarkable.

The investigation revealed a white blood cell count (WBC) of $6.79 \times 10^9/L$, with neutrophils of $2.69 \times 10^9/L$ and lymphocytes of $2.91 \times 10^9/L$ which were within the normal ranges. Haemoglobin level was 10.4 g/dL, while platelet count was $336 \times 10^9/L$. Her C-reactive protein was 4.8 mg/L and erythrocyte sedimentation rate was 104 mm/hr. Liver function tests, including alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (gamma-GT) were within normal limits. Renal functions were normal. Immunological tests indicated a positive antinuclear antibody (ANA) titer of 1:1280 with nuclear fine speckled pattern, and a negative dsDNA. Mantoux test and sputum AFB were negative. Imaging studies revealed no perihilar or hilar shadows on chest X-ray, a normal-sized liver, spleen, and kidneys on abdominal ultrasound, and suspicious axillary and inguinal lymphadenopathy on contrast-enhanced computed tomography (CECT) scan of the chest, abdomen, and pelvis. Additionally, ultrasound scan of the neck revealed enlarged lymph nodes at the anterior level I and bilateral levels II, III, IV, and posterior triangle. Some lymph nodes exhibited altered architecture with replaced fatty hilum and scattered intra-nodal vascularity. No perinodal collections or abscess formation were noted.

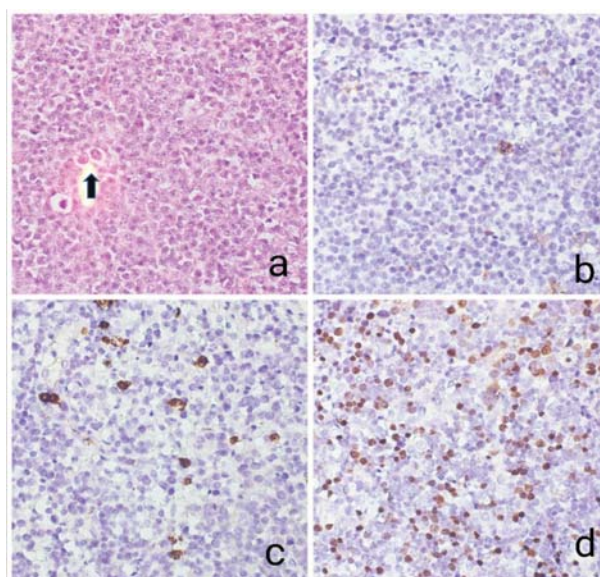


Figure 1.

1a) H and E staining of the Lymph node biopsy. The arrow shows Hodgkin Reed-Sternberg (HRS) cell with oval multi-lobulated nuclei, vesicular chromatin, prominent nucleoli and abundant cytoplasm.

1b) Immunohistochemistry showing Membrane and Golgi staining of large cells with CD 30. (Strong brown staining-HRS cells are universally positive to CD30).

1c) Immunohistochemistry showing Membrane and Golgi staining of large cells with CD 15. (Brown staining, less intense and more variable-HRS cells are variably positive to CD15).

1d) Immunohistochemistry showing weak nuclear positivity in large cells with PRAX5 (Weak brown staining-HRS cells show weak expression of PRAX5).

Her blood picture showed evidence of viral infection/inflammation with few reactive lymphocytes and neutrophil toxic changes. Bone marrow biopsy showed a reactive marrow with no evidence of non-Hodgkin's lymphoma (NHL) infiltration. A lymph node biopsy was performed from the right-sided submental lymph node. The report concluded that the appearances were indicative of Hodgkin lymphoma due to the presence of Reed Sternberg cells in H and E stain. According to the immunohisto-chemistry report, large cells showed CD 30 and CD 15 membrane and golgi positivity with PAX 5 weak nuclear positivity, along with background T and B lymphocytes (Figure 1).

Based on the histological features of lymph nodes, the patient was diagnosed as having Classic Hodgkin lymphoma. She was taken over by the hemato-oncology team and was started on chemotherapy following which the skin rash subsided.

Discussion

Hodgkin lymphoma (HL) is a neoplasm arising from B lymphocytes which affects men more than women. It has a bimodal age distribution with the first peak around 20 years and a second peak at ages over 50 years. Diagnostic tumor cells in classic HL (CHL) are the Hodgkin Reed Sternberg (H-RS) cells that have a B-cell origin. H-RS cells originate in the germinal center and they are clonally rearranged with unfavorable mutations of immunoglobulin genes, which lead them to inhibit apoptosis leading to systemic lymphoma disease.⁴ While the hallmark of HL is lymphadenopathy, it can present with extra nodal involvement, including cutaneous manifestations.

Cutaneous manifestations of HL have been divided into two groups; specific or non-specific. Specific lesions are rare, and caused by direct infiltration of the skin by malignant cells. The more frequent are the, nonspecific/paraneoplastic lesions, which includes hyperpigmentation, pruritus, prurigo, alopecia, eczema, erythema nodosum, and ichthyosiform atrophy.^{1,5} Exaggerated reaction to insect bite is infrequently described in patients with haematological neoplasms like chronic lymphocytic leukemia and Mantle cell lymphoma.^{6,7} Immunodeficiency plays a role in its pathogenesis; however, the exact pathogenesis is not yet known.⁶

Papular urticaria is the result of hypersensitivity to insect bites such as mosquitoes, gnats, fleas, mites, and bedbugs, characterized by symmetrically distributed pruritic papules and papulovesicles.⁸ Hypersensitivity to mosquito bites, characterized by intense cutaneous symptoms like erythema, bullae, ulcers, and scar formation in association with Hodgkin lymphoma has been rarely reported.⁹

The recognition of cutaneous involvement in HL can be challenging due to its variable clinical presentations and, the lesions being attributed to common skin conditions. A patient presenting with chronic pruritus being treated as prurigo nodularis for two years unresponsive to conventional treatment, was eventually diagnosed as Hodgkin lymphoma.¹⁰ This highlights the importance of considering malignancies in patients with chronic dermatological conditions as in our case. Clinicians should be vigilant to follow up such patients for any new developments as lymph nodes even though constitutional symptoms are absent.

While ANA positivity is a characteristic feature of autoimmune diseases and connective tissue disorders, the nucleolar pattern has been found to be associated with malignant diseases.¹¹ It has also been reported that ANA with a nucleolar pattern was associated with

a significant reduction in overall survival in patients with leukemia.¹² This suggests that ANA patterns can serve as a prognostic marker in hematological malignancies. The association of ANA with NHL has been studied, which has suggested that the frequency of ANA in NHL patients may vary depending on the histological subtype of the lymphoma.³ For example, certain subtypes like follicular and mantle cell lymphomas may exhibit higher frequencies of ANA compared to others, specifically those targeting components of the cell nucleus.³ These ANA patterns include homogeneous, speckled, and nucleolar types. The association of ANA with HL has not yet been studied.

Conclusion

This case highlights the importance of considering underlying hematological malignancies including HL as a differential diagnosis of unusual or refractory dermatological conditions. ANA positivity in a young patient needs high vigilance for hematological malignancies like NHL and rarely, HL, without attributing it alone to autoimmunity.

Author declaration

Consent

Informed written consent was obtained from the patient for publication of this case report.

Competing interests

The authors declare that there are no conflicts of interest.

Author contribution

HRKKM wrote the manuscript. SB made corrections and edited the manuscript.

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